THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 40

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SU S. WANG

Appeal No. 93-3083
Application 07/684,520[1]

ON BRIEF

Before CAROFF, WILLIAM F. SMITH and ELLIS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal from the final rejection of claims 1 through 6 and 8 through 19. Claim 7 has been indicated to be allowable by the examiner.

[1] Application for patent filed April 15, 1991. According to appellant, the application is a continuation of Application 07/192,349, filed May 10, 1988, now abandoned.

Claims 1 and 15 are illustrative of the subject matter on appeal and read as follows:

1. A process for producing thymosin α_1, or a biologically active analog or fragment thereof by solid-phase peptide synthesis, comprising the steps of (a) temporarily chemically protecting the reactive amino group at the alpha-position, and any other reactive groups, other than beta carboxylic acid group, on the C-terminal amino acid of thymosin α_1 peptide with 4-methoxybenzyloxycarbonyl; (b) chemically bonding the protected C-terminal amino acid via the unprotected carboxylic acid (-COOH) group thereof to a resin support; (c) chemically deprotecting the reactive amino group of the resin-bound protected amino acid by acidolytic cleavage using liquid trifluoroacetic acid; (d) chemically coupling via a peptide bond the next amino acid in the desired sequence by contacting the resin-bound amino acid from step (c) with the next amino acid in the desired sequence with all of the reactive groups thereof, other than the carboxylic acid group at the alpha-position, chemically protected with 4-methoxybenzyloxycarbonyl, in the presence of a coupling agent; (e) chemically deprotecting the reactive amino group of the coupled amino acid from step (d) by acidolytic cleavage using liquid trifluoroacetic acid; (f) continuing the synthesis by repeating steps (d) and (e) with successive amino acids in the desired sequence being added one at a time until the total desired sequence of the protected peptide is built up on the resin; and (g) cleaving the protected peptide from the resin support and deprotecting protected reaction groups using liquid trifluoroacetic acid; whereby the volume of liquid trifluoroacetic acid used in steps (c) and (e) is substantially reduced as compared to the volume of liquid trifluoroacetic acid required in steps (c) and (e) when the alpha-amino groups of each successive amino acid are protected with tert-butyloxycarbonyl (BOC).

15. A process according to claim 1 for the large scale production of thymosin α_1 or its biologically active analog or fragment, in lot sizes of at least 10 grams, on a dry basis.

The references relied upon by the examiner are:

Wang ('788)	4,148,788	Apr. 10, 1979
McGregor	4,361,673	Nov. 30, 1982

Wang ('407)	4,855,407	Aug. 08, 1989
Eur. Pat. App. (Wang ('404))	0,200,404	Nov. 05, 1986

Gross et al. (eds.), The Peptides: Analysis, Synthesis, Biology, Vol. 3, pp. 15-19, 31-33, and 212-215, Academic Press, Inc., 1981. (Gross Vol. 3).

The references of record cited by Appellant and relied upon are:

Gary R. Matsueda et al. "New urethane protecting groups: The optically active 1-arylethoxycarbonyl group", in Peptides: Chemistry, Structure and Biology, Proceedings of the Fourth American Peptide Symposium, June 1-6, 1975, Mann Arbor Science Publisher, Inc., pp. 333-339. (Matsueda).

Jean-Luc Fauchere et al. "Differential protection and selective deprotection in peptide synthesis", in The Peptides: Analysis, Synthesis, Biology, Erhard Gross et al. (eds.), Vol. 3, pp. 203-252 (Academic Press, Inc., 1981). (Fauchere).[2]

Erhard Gross et al. (eds.), The Peptides: Analysis, Synthesis, Biology, Vol. 2, pp. 101-108 (Academic Press, Inc., 1980). (Gross Vol. 2).

Claims 1 through 6 and 8 through 19 stand rejected under 35 U.S.C. § 103 as unpatentable over any of Wang ('788), Wang ('404), or McGregor, in view of Gross Vol. 3. Claims 1

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[2] The reference by Fauchere is a chapter from Volume 3 of The Peptides: Analysis, Synthesis, Biology, edited by Erhard Gross, from which are derived the references cited by the examiner as Gross Vol. 3. The chapter by Fauchere includes pages 212-215, which are relied upon by the examiner. In other words, both Appellant and the examiner rely upon the same reference in support of their respective positions. Appellant relies upon the entire chapter, pages 203-252, while the examiner only relies upon pages 212-15 of this chapter.

through 6 and 8 through 19 also stand rejected under the judicially created doctrine of obviousness-type double patenting over Wang ('407) in view of Gross Vol. 3. We shall affirm both grounds of rejection.

BACKGROUND

Solid phase peptide synthesis is a process of chemically synthesizing peptides with a specific, desired sequence of amino acids by sequentially adding amino acid substituents to an initial amino acid bound to a solid support. During the addition reaction, most reactive groups on the incoming amino acid and on the nascent peptide must be masked by protecting groups in order to inhibit side reactions which would result in undesirable by-products. One of the reactive groups that must be masked is the alpha amino group of the incoming amino acid. Many protecting groups for solid phase peptide synthesis have been developed, including 4-methyoxybenzyloxy-carbonyl (MOZ) and tert-butyloxycarbonyl (BOC). Following addition of the incoming amino acid to the nascent peptide chain, the protecting group of the alpha amino group is removed (deprotection) in order to ready the peptide for addition of the next amino acid. The invention of the instant application is a method of solid phase peptide synthesis of the peptide thymosin

α_1, using MOZ as a protecting group for the reactive alpha amino group of the amino acid substituents added to the peptide during synthesis.

DISCUSSION

Rejection Under 35 U.S.C. § 103

Claims 1 through 6 and 8 though 14

Each of Wang ('788) and Wang ('404) teach solid phase synthesis of thymosin α_1, using BOC as the alpha amino protecting group. See Wang ('788), Example 56, and Wang ('404), Example 2. Wang ('788) teaches deprotection using TFA, column 5, lines 15-18, and Example 56. Wang ('404) teaches the advantage of deprotecting using a mixture of TFA, hydrogen bromide, anisole and thioanisole at page 12, lines 20-24. McGregor teaches solid phase synthesis of thymosin α_1 fragments, column 1, lines 50-68, by solid phase synthesis, column 3, lines 4-40, with deprotection using TFA, column 3, lines 10-12. McGregor also lists MOZ as one of the alpha amino protecting groups "well known to the art." See column 3, lines 58-62 and column 3, line 68 to column 4, line 1.

While none of these references explicitly teaches solid phase synthesis of thymosin α_1 using MOZ as the alpha amino

protecting group, Gross Vol. 3 does teach that (1) MOZ was known in the art as a protecting group (pages 17-18), and (2) MOZ was known to be cleaved from an amino acid 250 times as quickly by TFA than BOC (Table 1 on pages 212-213). Furthermore, the reference teaches the implications of this increased sensitivity to TFA cleavage were appreciated by those of ordinary skill in the art (page 17: "the 4-methoxybenzyloxycarbonyl (Moz) group is readily cleaved by cold trifluoroacetic acid providing a clear selectivity within this class of amino protecting groups").

From these teachings, we agree with the conclusion of the examiner that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the MOZ protecting group taught by Gross Vol. 3 in the solid phase thymosin α_1 synthesis process taught by any of Wang ('788), Wang ('404), or McGregor since the skilled artisan would have expected that the MOZ group would be more efficiently deprotected by TFA than the BOC group of the prior art processes due to the 250-fold higher rate of cleavage of MOZ compared to BOC.

Appellant argues that the claimed invention is not obvious over the prior art because the substitution of MOZ for BOC provides an unexpected advantage, i.e., increased sensitivity to deprotection with trifluoroacetic acid (TFA), allowing

synthesis using lower concentrations of TFA, with resulting economic and environmental advantages. The issue to be decided, therefore, is whether the increased sensitivity of the MOZ protecting group to TFA cleavage was unexpected in view of the prior art.

Appellant argues that prior to the instant invention, those of ordinary skill in this art considered the MOZ and BOC protecting groups to be essentially equivalent in the property of acid hydrolysis; i.e., ease of deprotectability. In support of this position, Appellant argues that Fauchere, which reviewed protecting groups used in solid phase synthesis, divided the protecting groups into three categories based on their susceptibility to acid cleavage and placed MOZ and BOC in the same category of protecting groups; thus showing that the art recognized MOZ and BOC as interchangeable (Fauchere, pages 219-223). In support of this position, Appellant cites Gross Vol. 2, as teaching that MOZ is "deprotected under the same acidolytic conditions and at essentially the same rate[] as the tert-butyloxycarbonyl group [BOC]" (page 107). Appellant cites as further support for the so-called art-recognized interchangeability of MOZ and BOC the disclosure in Gross Vol. 2 that BOC was the preferred alpha amino protecting group for solid

phase peptide synthesis (Gross Vol. 2, pages 101-102), and the lack of kinetic studies in the art measuring the relative labilities of MOZ and BOC to different acid deprotecting agents.

Further, Appellant argues that those skilled in the art recognize that the rate of cleavage of protecting groups can differ based on substrates and reaction conditions and therefore the results shown in Table I of Gross Vol. 3/Fauchere cannot be assumed to be valid for the substrates and reaction conditions of the claimed process, especially since the TFA cleavage data in the table were derived using an assay that was less than ideal for measuring the rate of TFA cleavage of BOC (Matsueda, page 334). In fact, Appellant argues, Figure 1 of the instant specification shows that only a ten-fold difference in reaction rate was observed, not the 250-fold difference disclosed in Table I of Gross Vol. 3/Fauchere. Appellant concludes that, based on this art-recognized equivalency, the increased sensitivity of MOZ to TFA cleavage shown in the instant application is unexpected, and therefore unobvious as a matter of law.

Having carefully considered Appellant's position on the matter, we hold that a person of ordinary skill in the art would have expected MOZ-protected amino acids to be more sensitive to TFA than BOC-protected amino acids. Thus, considering the

evidence of record as a whole, we find no error in the examiner's determination that the subject matter on appeal would have been obvious under 35 U.S.C. § 103.

Appellant places heavy reliance on the division by Fauchere of protecting groups into three sets based on their sensitivity to acid hydrolysis. Appellant's position that Fauchere places MOZ and BOC in the same set, however, is unsupported by the record. On page 221, Fauchere teaches that BOC is a member of the second set (cleavable by concentrated TFA) but nowhere does Fauchere disclose which group MOZ is considered to belong to. Appellant's arguments based on Fauchere as evidence of the so-called art-recognized interchangeability of MOZ and BOC are therefore unpersuasive.[3]

In addition, the division by Fauchere of protecting groups into different sets was done, not to identify protecting groups which are functionally equivalent, but to identify protecting groups which could be used <u>together</u>, <u>at the same time</u>. During solid phase synthesis, the alpha amino group of each incoming amino acid must start out protected, then be deprotected

[3] At page 7 of the Reply Brief filed May 12, 1993, Appellant cites page 47 of "Gross et al." as showing the asserted similar categorization of MOZ and BOC. However, page 47 of this reference is not a part of the record of this case. Thus, it cannot be relied on to support Appellant's position.

after the amino acid is stably attached to the nascent peptide chain. Reactive groups in the amino acids other than the alpha amino group must be complexed with a different protective group, so that they can be protected and remain protected (in order to avoid undesirable side reactions) even in the conditions under which the alpha amino group is deprotected. In an iterative process like solid phase peptide synthesis, a couple-of-hundred-fold difference in reaction rate may be inadequate to allow use of two protecting groups simultaneously, since the less reactive group will still be deprotected to some degree during each round of amino acid addition, leading to an unacceptably high level of error after all the rounds of reaction are completed. Thus, even if Fauchere had put both MOZ and BOC in the same category with regard to acid hydrolysis, such a categorization could not be taken to mean, as Appellant would have it, that Fauchere considered MOZ and BOC to be interchangeable.

As further support for the so-called art-recognized equivalence, Appellant cites Gross Vol. 2 for the proposition that MOZ is deprotected under the same acidolytic conditions and at essentially the same rate as BOC. This argument is also unpersuasive, since it is apparent that the reference refers to cleavage by HBr or HCl, not TFA. Table I of Gross Vol.

3/Fauchere (pages 212-213) shows that cleavage of MOZ on treatment with HBr or HCl is only 1.2 to 1.6 times as rapid as cleavage of BOC under the same conditions. Appellant has not pointed to any disclosure in the prior art to support an interpretation that Fauchere intended to characterize the 250-fold difference in TFA cleavage rates as "essentially the same rate." Appellant's interpretation of Fauchere is thus accurate only with respect to HBr or HCl acidolytic conditions, not to TFA acidolytic conditions.

Appellant also argues that the so-called preference in the prior art for using BOC instead of other protective groups to protect the alpha amino group of amino acids, along with the lack of kinetic studies comparing cleavage rates of MOZ and BOC, are further evidence supporting the proposition that the art recognized BOC and MOZ as equivalents. Neither point is persuasive. First, the kinetic studies which Appellant believes were not done were in fact carried out; the results are shown in Table I of Gross Vol. 3/Fauchere. Second, it is unclear how Appellant's position that the art evinced a distinct preference for one particular protecting group logically leads to the conclusion that the art recognized that such a preferred protecting group was functionally equivalent to another

protecting group. If the two protecting groups were recognized as equivalents, it would seem reasonable to expect the two to be used at roughly the same frequency. The alleged predominance of BOC over MOZ would more reasonably be taken to indicate that BOC was considered preferable to MOZ, not equivalent to it. However, nothing in this record shows that even if a preference for BOC over MOZ existed, a point not conceded, that the preference was related to acid sensitivity as opposed to such extraneous factors as cost and availability.

Appellant also argues that any apparent difference in the rate of acid hydrolysis of MOZ and BOC shown in the prior art would not have been expected to apply in solid phase peptide synthesis because: 1) the rates of such reactions are highly dependent on the peptide substrate and reaction conditions; 2) Matsueda used a less-than-ideal assay for comparing the rates of MOZ and BOC hydrolysis; and 3) the actual difference in reaction rates turned out to be only ten-fold different, not 250-fold as would have been predicted. These arguments are not persuasive.

First, Fauchere expressly states that the "[k]inetic measurements of Homer et al. (1965) as well as those of Meienhofer (1966) with benzyloxycarbonyl- or substituted benzyloxycarbonylamino acids or small peptides showed . . . that

the rate of splitting was rather insensitive to the nature of the amino acid or peptide . . ." (sentence bridging pages 214 and 215). Thus, the record shows that those in the art considered results of MOZ cleavage obtained with one peptide substrate predictive for cleavage of MOZ with other peptide substrates.

Second, Appellant cites Matsueda (page 336) for support for the position that the rate of deprotection of MOZ- and BOC-protected amino acids depends on solvent conditions. However, the passages pointed to by Appellant relate to the cleavage of a different protecting group, α-2,4,5-tetramethylbenzyloxycarbonyl (TmZ), not MOZ or BOC. See pages 335-336: "The effect of different solvents on the rate of deprotection of TmZ-Gly-OEt was studied by a different experimental protocol. . . . It would follow, therefore, that the rate of deprotection depends on solvent and acid strength as shown in Figure 1." (the caption to Figure 1 reads: "Figure 1: Solvent effects on the extent of deprotection of TmZ-Gly-OEt by TFA in: [different solvents]").

Finally, Appellant argues that Figure 1 of the specification shows that the actual difference in cleavage rates between MOZ and BOC is only ten times, not 250 times, under the particular reaction conditions used. Appellant does not explain how the "ten-fold" figure was derived from the data in Figure 1.

In fact, the difference appears closer to fifty-fold; the specification states that a MOZ-protected peptide was deprotected by 10% TFA with a half-life of 0.3 minutes (page 13, lines 14-15), while Figure 1 shows that a BOC-protected peptide treated with 10% TFA reached 50% deprotection after about 15 minutes, thus showing a fifty-fold difference in half-life. Whether the actual difference is ten-fold or fifty-fold, however, the reaction rate actually observed under the reaction conditions used does not suffice to establish the unobviousness of the claimed process. At best, those results indicate that the precise increase in the cleavage rate obtained from using MOZ in place of BOC will vary depending on the particular conditions and materials used. "Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness." In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-652 (Fed. Cir. 1985).

Claims 15 through 19

Claims 15 through 19 specify the scale of the procedure claimed in claim 1. Appellant argues that the invention of claims 15 through 19 is patentably distinguishable from the cited prior art because "the use of MOZ as the alpha-amino [protecting]

group has provided a solution to many of the problems that have hindered the process of large scale peptide synthesis" (Appeal Brief, page 14). Appellant's argument for the separate patentability of claims 15 through 19 is not persuasive.

Appellant has not established on this record that prior art procedures of peptide synthesis using BOC are limited to a particular scale by technical constraints. Rather, as understood, the benefits of scale provided by using MOZ in place of BOC flow, directly or indirectly, from the more efficient use of TFA in the deprotection steps of the synthesis. However, the fact that substitution of MOZ for BOC would allow enhanced deprotection using TFA is expected, not unexpected, since the increased sensitivity of MOZ to TFA was known in the art.

Obviousness-type Double Patenting Rejection

The examiner also rejected the claims for obviousness-type double patenting over Wang ('407) in view of Gross Vol. 3. Wang ('407) is the U.S. counterpart application to the European Patent Application Wang ('404).

The focus of an obviousness-type double patenting determination must be on the respective claims. Wang ('407) claims solid phase synthesis of thymosin α_1 using alpha amino

protecting groups broadly and carrying out the protection and deprotection steps in TFA. See, e.g., claim 21 of Wang ('407). As discussed above, Gross Vol. 3 teaches that (1) MOZ was a well-known protecting group, (2) MOZ was known to be cleaved 250 times as quickly by TFA than BOC, and (3) this increased sensitivity to TFA cleavage was appreciated by those of skill in the art to provide "a clear selectivity" for MOZ. Thus, we agree with the examiner's conclusion that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the MOZ protecting group taught by Gross Vol. 3 in the solid phase thymosin α_1 synthesis process claimed by Wang ('407). Appellant's position on this matter is the same as that presented in response to the rejection under 35 U.S.C. § 103. Thus, we affirm this rejection for the same reasons discussed above in the rejection under 35 U.S.C. § 103.

The decision of the examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

MARC L. CAROFF)
Administrative Patent Judge)
)
) BOARD OF
WILLIAM F. SMITH) PATENT APPEALS
Administrative Patent Judge) AND
) INTERFERENCES
)
JOAN ELLIS)
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